REMARKS

Claims 99-100, 103-107, 119, 121 and 128-129 were previously pending. Applicants have amended claim 99 to recite "A method for enhancing cellular uptake of an oligonucleotide administered as an aerosol into a lung of a mammal by including 2'-O-methoxyethyl and 5-methylcytosine modifications in said oligonucleotide, said method comprising..." to clarify the claimed subject matter. Support for this amendment can be found throughout the specification as filed, for example, at Example 3, Tables 2 and 3, where oligonucleotides comprising 2'-O-methoxyethyl and 5-methylcytosine modifications had enhanced cellular uptake when administered as an aerosol into the lung as compared to oligonucleotides of the same sequence without 2'-O-methoxyethyl and 5-methylcytosine modifications.

In view of the above, Applicants submit that no new matter is added and request entry of these amendments. After entry of these amendments, claims 99-100, 103-107, 119, 121 and 128-129 will be pending and under consideration.

35 U.S.C. § 103(a) – Obviousness

All pending claims remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 2. The Office asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-methylcytosine modifications. *See Office Action* at 5. The Office asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

Lack of Evidentiary Support for Examiner's Factual Assertions

In response to Applicants' previous arguments, the Office asserts that "[o]ne would have been motivated to incorporate such 2'-O-methoxyethyl or 5-methylcytosine modifications ... because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target," that "**each** of the modifications were known to enhance the delivery of antisense compounds...," and that "**each** of the instantly recited chemical modifications were known in the art to benefit the stability of

antisense oligonucleotides," as evidenced by the cited references. *Office Action* at 6, 6-7 and 7, (emphasis added).

As Applicants have previously noted, Applicants are not aware of anything in the record that supports the conclusion that inclusion of 2'-O-methoxyethyl (2'-MOE) or 5-methylcytosine modifications would have been expected to improve cellular uptake or stability of the oligonucleotides.

The Examiner's statement that "such" modification are taught by Nicklin et al. to confer increased uptake into cells is not accurate to the extent that the Examiner is asserting that Nicklin teaches that 2'-MOE or 5-methylcytosine modifications increase cellular uptake. Rather, Nicklin states that unspecified "analogues" of oligonucleotides can enhance cellular uptake, enhance target binding affinity, and increase stability. *Nicklin* at page 2. When 2' sugar modifications in particular are discussed, Nicklin teaches that they are added "to increase target binding affinity" – not to increase cellular uptake. *Id.* at page 3.

Similarly, the statement that "each" modification is known to enhance uptake or stability is not accurate. While some modifications were thought to enhance uptake and stability, (e.g. backbone modifications), 2'-MOE or 5-methylcytosine modifications were not among them. The Examiner has not pointed to any passage to support the assertion that 2'-MOE or 5-methylcytosine modifications increase cellular uptake or stability.

An expert in the field has offered the following opinion regarding what one of skill in the art would have known about 2'-MOE and 5-methylcytosine modifications at the time of filing:

> 3. I am informed that the Examiner has asserted that at the time of the above captioned invention, a person of ordinary skill in the art would have been motivated to incorporate 2'-O-methoxyethyl and 5-methylcytosine modifications into the oligonucleotides of Nyce et al. (WO 96/40266) because Nicklin et al. (WO 96/09633) teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target.
>
> 4. I have reviewed Nicklin et al. and do not find support for the assertion that incorporation of 2'-O-methoxyethyl modifications would result in increased uptake of a nucleic acid into cells. The specific section of Nicklin asserted to teach that modifications of antisense oligonucleotides confer increased uptake into cells does not suggest that 2' modifications are capable of increasing cellular uptake. Rather, Nicklin et al. confirm, as was understood at the time, that

> modification of the 2' position of the nucleotide sugar increases target binding affinity. *Nicklin* at pages 2-3.
>
> 5. It is my expert opinion that at the time of the invention, one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. At the time of the invention, the inclusion of one or more, a majority, or even full 2'-O-methoxyethyl modifications in a nucleic acid was thought to potentially increase stability of the nucleic acid and/or increase affinity of the nucleic acid to a complementary strand. In my experience, the distribution of oligonucleotide following parenteral dosing of oligonucleotides containing 2'-O-methoxyethyl modifications was essentially identical to the first generation modified oligonucleotides containing only phosphorothioate backbone modifications. As a result, I and my colleagues concluded that the phosphorothioate backbone guided distribution and uptake, not 2'-O-methoxyethyl modification.
>
> *Declaration of Richard Geary, Ph.D.* (submitted with response on May 6, 2009) (emphasis added).

The above statements of an expert in the field clearly refute the conclusion reached by the Examiner regarding the teachings of Nicklin. et al. At the time of filing, 2'-MOE or 5-methylcytosine modifications were only thought to increase target binding, and were not thought to improve cellular uptake.

For these reasons, Applicants maintain that none of the above statements by the Examiner are supported by the evidence of record, and therefore are statements by "official notice." *See, e.g., In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). Applicants request documentary evidence in support of the noticed statements, in accordance with M.P.E.P. § 2144.03.C.. In particular, Applicants request that the Examiner point to the portion of the reference(s) that support the assertion that 2'-MOE sugar modifications or 5-methyl cytosine modifications were known to increase cellular uptake or enhance stability. Disclosure that "modifications" or "analogues" generally were known to have these properties is not evidence that these particular modifications were known to affect uptake or stability.

In response to Applicants' arguments, the Examiner asserts that modifications that increase binding to the target and/or stability of the oligonucleotide would result in an increase of

uptake compared to non-modified oligonucleotides. *Office Action* at page 10. This argument fails for at least two reasons.

First, it is not apparent how increased target binding affinity could affect cellular uptake since target binding only occurs after cellular uptake (target binding occurs inside the cell). Absent any evidence to support the conclusion that increased target binding increases cellular uptake, this assertion is unsupported and therefore is a statement by "official notice." *See, e.g., In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). Applicants request documentary evidence in support of the noticed statement, in accordance with M.P.E.P. § 2144.03.C..

Second, as discussed above, the Examiner's assertion throughout the Office Action that 2'-MOE or 5-methylcytosine modifications were known in the art to benefit the stability of antisense oligonucleotides is unsupported. And even if *arguendo* 2'-MOE or 5-methylcytosine modifications result in increased stability, it would not affect uptake into the cell if the stability is due to interactions with the target mRNA or resistance to intracellular nucleases since this would only occur after cellular uptake. Absent any evidence to support the conclusion that 2'-MOE or 5-methylcytosine modifications improve stability, and that this stability increases cellular uptake, these assertions are unsupported and therefore are statements by "official notice." *See, e.g., In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). Applicants request documentary evidence in support of the noticed statements, in accordance with M.P.E.P. § 2144.03.C..

Finally, Applicants note that the data presented in Tables 2 and 3 are a measure of total oligonucleotide taken up by the cell – both the metabolites and parent oligonucleotide are included in the measurements. *See Specification* at page 68, lines 11-16 (note that the Specification recites "Table 1 and Table 2" when it should recite "Table 2 and Table 3".) This means that even *if* oligonucleotide degradation inside the cell is affected by the recited modifications, it will not change the overall concentration of oligonucleotide reported. Stated differently, the data reported in Tables 2 and 3 allows a comparison of the amount of oligonucleotide that enters the cell, independent of its stability and metabolism once it is inside the cell.

Unexpected Results

Even if a *prima facie* case of obviousness has been established, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results which are sufficient to overcome any *prima facie* case of obviousness. Applicants have found that incorporating 2'-MOE nucleosides enhances the uptake of oligonucleotides into cells of the lungs when administered into the lung, by as much as 300%. Applicants are not aware of a single piece of evidence in the record that supports the conclusion that this result was expected, and an expert in the field has stated in a declaration that it was in fact unexpected at the time of the invention. *See Declaration of Richard Geary, Ph.D.* at ¶6. ("It is my expert opinion that at the time of the invention, this result was unexpected.")

The Office responds to Applicants' assertion of unexpected results by arguing that "one would reasonably expect enhanced uptake based upon the teachings of Nicklin with regards to modifications including 2'-O-modifications;" and that "based upon the combined teachings of the prior art, one would expect for the instant modifications to enhance stability of the oligonucleotide" which would lead to enhanced uptake. *Office Action* at page 12 (emphasis added).

As explained above, these assertions – that the prior art teaches 2'-O-modifications enhance uptake or enhance stability – are unsupported by the record and contrary to the expert declaration of Dr. Richard Geary. In addition, even if *arguendo* 2'-O-modifications enhance uptake or enhance stability, there is no evidence of record that these modifications would be expected to improve cellular uptake by as much as 300% when administered as an aerosol into the lung. In fact, the evidence of record that this result is unexpected to those of skill in the art. *See Declaration of Richard Geary, Ph.D.* at ¶6.

The Examiner acknowledges that if there is a motivation to include 2'-MOE modifications in the prior art, there can still be unexpected results. *Office Action* at page 13 (stating that a conclusion to the contrary is "in error"). However, the Examiner states that Applicants' reliance on the 300% improvement in uptake is "arguing a limitation that is not claimed," and that one would expect "any level of uptake more than unmodified oligonucleotides, when incorporating 2'-MOE modifications in view of the teachings of the prior art." *Id.* These arguments are flawed for at least two reasons.

First, it is well-established that unexpected results do not have to be recited in the claims to be relied on. If the unexpected properties of a compound or method must always be recited in a claim, they would not be "secondary considerations" which can overcome a *prima facie* case of obviousness, but rather would always be limitations which are considered as part of the *prima facie* case. *See, e.g. M.P.E.P. §2145.* Rather, the unexpected results that flow from the claimed composition or method need only be unexpected in view of the closest cited reference. *See M.P.E.P. §716.02.* Applicants invite the Examiner to cite authority to support the Examiner's implied statement that an unexpected result must be recited in a claim to be relied on.

Second, as discussed above, there is no evidence of record which supports the Examiner's statement that one would expect "any level of uptake more than unmodified oligonucleotides, when incorporating 2'-MOE modifications in view of the teachings of the prior art." And, even if there were some support for this statement, it does not address Applicants' assertion that the results in Tables 2 and 3 (as much as 300% increase) are unexpected – "any level of uptake" is not sufficient to reject the observed increases as "expected."

Finally, the Examiner argues that the unexpected results are not commensurate in scope with the claims. Applicants respectfully disagree for the reasons stated in previous responses.

However, without acquiescing to the Examiner's arguments, and solely in the interest of advancing prosecution, Applicants have amended claim 99 to recite "A method for enhancing cellular uptake of an oligonucleotide administered as an aerosol into a lung of a mammal by including 2'-O-methoxyethyl and 5-methylcytosine modifications in said oligonucleotide, said method comprising..." to clarify the claimed subject matter.

In summary, Applicants submit that the cited references do not teach that the inclusion of 2'-MOE modifications would enhance cellular uptake of an aerosolized oligonucleotide delivered into the lung. Thus, even *if* the Office has established that one of skill in the art would have been motivated to include a 2'-MOE modification in the method of Nyce, a point Applicants do not concede, Applicants submit that the evidence of record establishes that the increased cellular uptake of the recited compounds is unexpected, and therefore the pending methods are not obvious in view of the cited references.

For at least the above reason, Applicants submit that the pending claims are patentable over the cited references. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

35 U.S.C. § 112, first paragraph – Written Description

All previously pending claims are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office argues that the specification does not support oligonucleotides 15 to 25 nucleotides in length with at least 10 2'-O-methoxyethyl modifications in combination with each cytosine being a 5-methylcytosine, or at least 10 to all but one nucleosides being 2'-O-methoxyethyl modifications. The Examiner asserts that Example 3 is "not representative of the instantly claimed genus of molecules having the instantly recited outcome." *Office Action* at page 15. The Examiner also asserts that "support is not evident in the instant specification for at least one phosphorothioate linkage as recited in claim 100." *Id.*

The proper test for satisfaction of the written description requirement is "[w]hether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1562-63, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (citations omitted). Applicants remind the Examiner that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." – conclusory statements are not sufficient. *M.P.E.P. §2163.*

The claimed method recites: "A method ... comprising: administering an aerosolized oligonucleotide into the lung of a mammal, wherein the aerosol particles have a size of about 1 to about 5 microns, wherein said oligonucleotide is 15 to 25 nucleotides in length, wherein at least 10 nucleosides in said oligonucleotide are 2'-O-methoxyethyl nucleosides, wherein each cytosine of said oligonucleotide is a 5-methylcytosine, and wherein said oligonucleotide is taken up by at least one cell type in the lung of the mammal."

The "Field of the Invention" is described as directed to "compositions and methods for the pulmonary delivery of oligonucleotide therapeutics and diagnostics, including antisense

oligonucleotides." *Specification* at p. 1, lines 12-15. The term "oligonucleotide" includes "oligonucleotides composed of naturally-occurring nucleobases, sugars and covalent intersugar (backbone) linkages as well as oligonucleotides having non-naturally-occurring portions which function similarly." *Id.* at p. 13, lines 25-29. "Other specific oligonucleotide chemical modifications are described in the following subsections. It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the following modifications may be incorporated in a single antisense compound or even in a single residue thereof, for example, at a single nucleoside with an oligonucleotide." *Id.* at p. 20, lines 18-24 (emphasis added). The specification then describes base modifications, including 5-methylcytosine, (p. 20, lines 32-34), sugar modifications, including 2'-MOE modifications (p. 23, lines 30-34) and modified linkages (backbones), including a phosphorothioate linkage (p. 24, line 32-33). Finally, the specification discloses that the invention includes chimeras "which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound." *Id.* at p. 31, lines 19-24 (emphasis added). In view of these disclosures, as well as additional specific examples throughout the specification, one of skill in the art would recognize that Applicants were in possession of the claimed invention at the time of filing.

In view of the above, Applicants request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not

reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Office's attention to the following patents or applications. Applicants encourage the Office to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

CONCLUSION

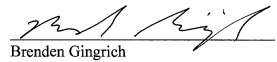
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/14/11

By: 

Brenden Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(858) 707-4000

11951028
092011